molecules and permit the human antigen presenting cells to produce one or more processed antigens;

(b) contacting the antigen presenting cells produced by step (a) with monoclonal human T cells having a T cell receptor specific for said specific T cell epitope and known HLA allele for said T cells under conditions sufficient for said T cells to respond to the processed antigen;

(c) determining the T cell response to the processed antigen, whereby the vaccine composition possessing an optimal response is selected;

(d) assessing the vaccine composition isolated in step (c) in one or more human subjects.

REMARKS

Reasons for Substitute Amendment

This Substitute Amendment is being file in lieu of the Amendment filed in response to the Office Action mailed, by Applicants, to the United States Patent and Trademark Office on November 25, 2002. The earlier reply was found to be not fully responsive to the prior Office Action mailed on June 24, 2002. However, because a bona fide attempt to reply to the prior Office Action was made, Applicants were given an opportunity to supply the correction in order to avoid abandonment. Consideration of this Substitute Amendment is respectfully requested.

Relationship of New Claims 23-34 to Cancelled Claims 1, 4-8, 11, 17 and 20-22

New Claim 24 is entered to replace Cancelled Claim 1 except that New Claim 24 recites two or more distinct vaccine compositions in the group each having one or more nucleic acid molecules encoding one or more antigens which comprise a specific T cell epitope and that the peptide in step b is a peptide encoded by one or more nucleic acid molecules encoding one or more antigens which comprise said T cell epitope. Support for New Claim 24 can be found throughout the specification, for example, at page 11, lines 8-15. No new matter has been added.

New Claims 25-27 are entered to replace Cancelled Claims 4-6. No new matter has been added.

New Claim 28 is entered to replace Cancelled Claim 7 except that New Claim 28 recites the method of Claim 24 wherein the level of human T cell response to the processed antigen is indicated by the level of release of one or more cytokines or level of lysis of the human antigen presenting cells. Support for New Claim 28 can be found throughout the specification, for example, at page 13, lines 7-8, and page 14, lines 3-5. No new matter has been added.

New Claim 29 is entered to replace Cancelled Claim 8 except that minor typographical errors were corrected in New Claim 29. Support for New Claim 29 be found throughout the Specification and in the originally filed claim. No new matter has been added.

New Claims 30 and 31 are entered to replace Cancelled Claims 21 and 22. No new matter has been added.

New Claim 32 is entered to replace Cancelled Claim 11 except that New Claim 32 recites two or more distinct vaccine compositions in the group each having one or more nucleic acid molecules encoding one or more antigens which comprise a specific T cell epitope. Support for New Claim 32 can be found throughout the specification, for example, at page 11, lines 8-15. No new matter has been added.

New Claims 33 and 34 are entered to replace Cancelled Claims 17 and 20. No new matter has been added.

New Claim 35 has been added to recite a method for optimizing the T cell response against a T cell epitope. Support for this claim can be found throughout the specification, for example, at page 8, lines 13-23. No new matter has been added.

Rejection of Claims 1, 4-8, 11, 17, and 20-22 Under 35 U.S.C. §112, second paragraph

Claims 1, 4-8, 11, 17, and 20-22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 1, 4-8, 11, 17, and 20-22 have been cancelled herein and are replaced by New Claims 24-35. Applicants will address the rejection as the Examiner may apply it to the New Claims 24-35.

Specifically the Examiner states that Claims 1 and 11 are unclear in the preamble because it is not clear as to whether "a defined T-cell epitope" is a single epitope, common to all

members of the group of vaccines, or whether this is a unique epitope for each of the members of the group.

Claims 1 and 11 have been cancelled herein and New Claims 24 and 32 clearly recite that the vaccine compositions within the group of vaccine compositions are distinct from each other and that each have one or more nucleic acid molecules encoding one or more antigens which comprise a specific T cell epitope. Thus, while the compositions assayed are distinct, they are characterized by a common epitope. Reconsideration and withdrawal of the rejection as it applies to these claims are respectfully requested.

Additionally, the Examiner states that in Claim 1, part (b) "defined peptide" lacks antecedent basis. Claim 1 has been cancelled and New Claim 24 does not contain the word "defined", thus rendering the rejection moot. Reconsideration and withdrawal of the rejection as it applies to this claim are respectfully requested.

Moreover, the Examiner states that Claim 7 is unclear in relation to base Claim 1. Claims 1 and 7 has been cancelled herein and the relationship between New Claims 24 and 28 have been clarified by Applicants. Reconsideration and withdrawal of the rejection as it applies to this claim are respectfully requested.

Rejection of Claims 1, 4-8, 11, 17, and 20-22 Under 35 U.S.C. §112, first paragraph

Claims 1, 4-8, 11, 17, and 20-22 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 1, 4-8, 11, 17, and 20-22 have been cancelled herein and are replaced by New Claims 24-35. Applicants will address the rejection as the Examiner may apply it to the New Claims 24-35.

To support this rejection the Examiner states that there was no original disclosure that the candidate vaccines in the group of vaccine compositions have "a defined T cell epitope", irrespective of whether such "defined" epitope is common to all members or is a unique epitope for each of the members of the group. Thus, according to the Examiner, the phrase "a defined T cell epitope" constitutes new matter.

The newly entered claims recite "a vaccine composition in a group consisting of two or more distinct vaccine compositions each having one or more nucleic acid molecules encoding one or more antigens which comprise a specific T cell epitope ...". Support can be found throughout the Specification. For example, at page 4, lines 13-14, Applicants state that "the T cells are T cell clones which are ***specific*** for a T cell epitope in at least one of the antigens." Additionally, Applicants state at page 10, lines 4-5, "preferably, the T cells are ***specific*** for a particular epitope within the antigen." Moreover, at page 11, lines 8-15, Applicants teach that "the T cell are clones which are ***specific*** for a particular epitope, and the vaccine composition includes at least one antigen which comprises the epitope or at least one nucleic acid molecule encodine at least one antigen which comprises the epitope. In this embodiment, response of the ***epitope-specific T cell clones*** to antigen-presenting cells which have been contacted with the experimental vaccine composition indicates that the vaccine composition is able to effect the presentation of the epitope on the surface of the antigen-presenting cells in combination with an MHC I or MHC II molecule." (emphasis added)

Therefore, no new matter has been added to the newly entered claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 5-8, 11, 17 and 20 Under 35 U.S.C. §103(a)

Claims 1, 5-8, 11, 17 and 20 are rejected under 35 USC 103(a) as being unpatentable over Tal *et al.* (U.S. 5,763,284)("Tal") in light of Sette *et al.* (Nature 328, 397 (1987))("Sette"). Claims 1, 4-8, 11, 17, and 20-22 have been cancelled herein and are replaced by New Claims 24-35. Applicants will address the rejection as the Examiner may apply it to the New Claims 24-35.

The Examiner states that Tal shows an assay essentially corresponding to the instantly claimed assays (col. 10, line 34 through col. 12, line 21). Tal describes an assay to identify peptides useful in eliciting a desired immune response conducted by the following steps:

a. Antigen presenting cells are contacted with a fusion polypeptide of the invention;

b. T cells carrying the T cell receptor specific to the fusion polypeptide are obtained such as from a T cell hybridoma of interest;

c. T cells carrying the T cell receptor specific to the fusion polypeptide are contacted with the antigen presenting cells of step 1;

d. After a suitable period of time, modulation of the activity of the T cells by the fusion polypeptide is measured.

Tal goes on to state that "these *in vitro* assays can be employed to select and identify peptide(s) that are capable of modulating the activity of T cell receptor." (See Tal col. 11, lines 53-64) Specifically, DNA sequences encoding either a library of random peptides or selected peptides can be cloned into expression vectors and used in the assay as described above.

The Examiner relies upon Sette as a secondary reference. The Examiner states that the exemplified polypeptide in examples 9 and 10 of Sette has a defined T-cell epitope. Therefore, according to the Examiner, candidate vaccines with defined T-cell epitopes would have been obvious.

Applicant's claimed invention is directed to a method for assessing the ability of a vaccine composition in a group consisting of two or more distinct vaccine compositions each having one or more nucleic acid molecules encoding one or more antigens which comprise a specific T cell epitope, to stimulate a monoclonal human T cell response, said method comprising the steps of:

(1) contacting human antigen presenting cells in culture with the vaccine composition, thereby, if one or more of the nucleic acid molecules are taken up and processed by said antigen presenting cells, producing one or more processed antigens;

(2) contacting said antigen presenting cells of step (1) with monoclonal human T cells having a T cell receptor specific for the peptide encoded by said nucleic acid molecule(s) encoding one or more antigens which comprise said T cell epitope and known HLA allele for said T cells under conditions sufficient for said T cells to respond to the processed antigen;

(3) determining the level of said T cells' response to the processed antigen; and, if the vaccine composition exceeds a predetermined level of said T cells' response,

(4) assessing the vaccine composition in one or more human subjects.

Applicants method is used to determine the efficacy of one or more distinct vaccine compositions in a group of vaccine compositions. For example, as taught by Applicants at page 15, lines 29-31, the distinct vaccine compositions include the same antigen(s), but different

vectors, adjuvants, concentrations, vehicles or excipients can be compared to determine the conditions necessary for optimal efficacy.

The efficacy of a vaccine for use in humans depends upon the ability of the vaccine formulation to elicit an immune response which is sufficient to provide protection against subsequent challenge with the pathogen. Tal only teaches an assay that can be used to determine if a polypeptide can be processed by antigen presenting cells to elicit a T cell response. However, Tal neither teaches how to prepare a vaccine composition based on the nucleic acid and/or polypeptide for use in humans, nor how to test the efficacy of a vaccine composition *in vitro*. In contrast, Applicants teach a method that uses an antigen, that elicits a predetermined level of T cell response, in an *in vitro* test to determine the human response to an experimental vaccine construct comprising said antigen, which would allow the rapid evaluation of large numbers of candidate vaccine compositions within a short period of time and at a reasonable cost, thereby increasing the possibility that effective vaccine compositions will be discovered.

Therefore, Applicants claimed invention is non-obvious over the prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,
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Dated: 4/2/3

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 4, lines 12 through 18 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Preferably, the vaccine composition includes at least one antigen which comprises a T cell epitope, and the T cells are T cell clones which are specific for a T cell epitope in at least one of the antigens. In one embodiment, the T cells are CD8+ T cells and the vaccine composition includes at least one antigen comprising [antigen] a CD8 epitope. In this embodiment, the T cell response to the processed antigen can be, for example, T cell proliferation, cytolysis of the antigen presenting cells or the production of one or more cytokines.